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10/638,210	08/07/2003	Dongxiao Zhang	EPIT-001	5792

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/638,210	ZHANG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/04,7/1/05,8/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed 6/26/06 is acknowledged and has been entered.

2. Applicant's election with traverse of Group I (claims 1-13), and species of the method steps of molecular modeling an antibody from a VH1-a1 allotype rabbit to identify surface exposed amino acid residues, comparing the rabbit antibody framework sequence to human antibody framework sequences to identify the most similar human antibody, and substituting surface exposed amino acid residues in the rabbit antibody with corresponding amino acid residues in the human antibody, where the substitutions are not in the D-E loop region in Applicant's said response filed 6/26/06 is acknowledged.

It is noted by the Examiner that replacing the N-termini of the rabbit heavy and light chain variable domains is replacing the FR1 domains (page 18 of the instant specification at lines 10-13).

The basis for Applicant's traversal is Applicant's assertion that a search of all the claims of the instant application would not be unduly burdensome to the Examiner.

It is the Examiner's position that regarding undue burden, the M.P.E.P. 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the Examiner may be prima facie shown if the Examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search."

The restriction requirement enunciated in the previous Office Action meets this criterion of serious burden and therefore establishes that serious burden is placed on the Examiner by the examination of additional Groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1 and 3-13 read on the elected species.

Upon consideration of the prior art, the search has been extended to include the species recited in instant claim 2.

Accordingly, claims 14-20 (non-elected groups II-IV) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-13 are currently being examined.

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 15 at line 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

4. The abstract of the disclosure is objected to because it contains a line of text below the paragraph. An Abstract should be one paragraph. Correction is required. See MPEP § 608.01(b).

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 11 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 11 recites "The nucleic acid according to claim 10" at line 1. This limitation lacks antecedent basis in base claim 10.

b. Claim 12 recites "The nucleic acid according to claim 19" at line 1. This limitation lacks antecedent basis. Applicant may note that the Examiner grouped Claim 12 with the elected invention because it depends upon claim 11, and non-elected claim 19 recites a computer readable medium.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-13 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20050048578 A1 (priority to 6/26/03).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

US 20050048578 A1 discloses a method of making a humanized rabbit monoclonal antibody that is less immunogenic in a human, said method comprising resurfacing a rabbit monoclonal antibody (mAb), including a VH1-a1 allotype, by surface alignment comparison, *i.e.,* by comparing the amino acid sequences of the heavy and light chain variable regions with the most homologous human germline antibody genes, then predicting the surface residues in FR1, FR2 and FR3 of the most homologous human antibodies, identifying the rabbit framework residues at homologous positions, and substituting framework amino acid residues that are exposed in the rabbit mAb with the corresponding framework amino acid residues from the human antibody.
US 20050048578 A1 discloses that the framework regions have high homology to human sequences, and that the finding that rabbit antibody sequences can be readily aligned with human sequences shows that rabbit antibodies may be altered without substantially changing the conformation of rabbit antibody molecules, and thus retain the affinities of the modified rabbit antibodies. US 20050048578 A1 discloses changing Cys 80 in a parent mAb to the amino acid residue (Phe) found at position 80 of the human antibody. US 20050048578 A1 discloses making the humanized rabbit antibodies without substantially changing the conformation of the antibodies and further discloses use of the CAMEL modeling method to predict backbone conformations of all six CDRs and well as FR regions, and the interchain contact residues are expected to be non-surface exposed amino acid residues. US 20050048578 A1 discloses that it is preferable to produce an antibody that specifically binds to its corresponding antigen with a binding affinity of 10^{-8} M or more. US 20050048578 A1 exemplifies identifying amino acid residues of the framework region of the parent antibody that are not proximal to a CDR and substituting only those amino acid residues that are not proximal to said CDR, and teaches the importance of certain framework residues proximal to CDRs in maintaining the conformation of the CDRs and the affinity of the antibody, and identifying those residues located close to CDRs that may need to be preserved as rabbit residues in the humanized antibodies (especially [0059], [0016], [0148]-[0155], Figures 3 and 5, claim 3).

With regard to the inclusion of claims 11and 12 in this rejection, although the art reference does not teach homozygosity at the VH locus, the claimed process appears to be the same since the art reference discloses comparison with heavy chain allotypes. With regard to the inclusion of claim 2 in this rejection, although the

art reference does not explicitly disclose identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1 and 3-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popkov *et al* (J. Mol. Biol. 325: 325-335, 2003, IDS reference) in view of Morea *et al* (Methods 20: 267-279, 2000, IDS reference).

Popkov *et al* teach that rabbit polyclonal antibodies have been used in diagnostic applications and that rabbit monoclonal antibodies may be useful in therapeutic applications as the HCDR3 length distribution is more similar to human than mouse antibodies. Popkov *et al* teach "The fact that the HCDR3 length distribution in rabbit antibodies is more similar to human than mouse antibodies is highly relevant for the generation of therapeutic mAbs from rabbit immune repertoires, since this region is conserved I the process of antibody humanization. As a consequence, humanized rabbit antibodies may be more closely related to human antibodies than humanized mouse antibodies." Popkov *et al* teach that rabbit mAbs selected from antibody libraries by phage display can be humanized while retaining both high specificity and strong affinity to the human antigen, and that the rabbit repertoire is an attractive alternative to the mouse antibody repertoire from the generation of mAbs to human antigens, since rabbits are evolutionarily distant from mice, are not negatively selected against epitopes displayed by the mouse antigen as are humanized and human antibodies that are derived from immune mice and thus often lack cross-reactivity between human and mouse epitopes, and since epitopes not immunogenic in mice might be immunogenic in rabbits. Popkov *et al* teach making the monoclonal antibodies in rabbits homozygous for a kappa allotype that produce higher levels of Vκ sequences lacking cysteine 80 that yield chimeric Fab with superior properties, an unpaired cysteine 80 being associated with lower selectable antibody diversity. Popkov *et al* teach one rabbit was homozygous for the VH1-a3 allotype. Popkov *et*

al teach rabbit monoclonal antibodies with binding affinities in the 400-500 pM range, *i.e.,* with a binding affinity of greater than 10^8 M^{-1} (see entire article, especially abstract, page 326 at column 1 through the last full paragraph, page 327 at column 1, first full paragraph, materials and methods, and last paragraph of article).

Popkov *et al* do not teach wherein the method of humanizing a rabbit monoclonal antibody is by resurfacing, including the limitations of the method recited in the instant claims.

Morea *et al* teach resurfacing by comparing the sequences of the variable domains of a non-human antibody with human variable domains, and substituting the surface framework residues of the non-human antibody with the corresponding human residues. Morea *et al* teach maintaining antigen specificity and affinity of the non-human antibody that is resurfaced. Morea *et al* teach that key-site surface residues should not be changed, nor should antigen binding contact sites, nor should any residues be changed that alter the structure of the antigen binding site. Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and that, as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged and consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced antibody are similar to those of the starting antibody. Morea *et al* teach molecular modeling of the variable domains, including the framework regions using as a template the domain of known structure with the highest sequence identity with the target domain (see entire article especially page 276 at column 2 starting at the first full paragraph and continuing through the first full paragraph on page 277, and page 272 at column 1 through page 274 at the first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used in the method of humanizing a non-human antibody by resurfacing the rabbit monoclonal antibody taught by Popkov *et al.*

One of ordinary skill in the art at the time the invention was made would have altered the method of Morea *et al* to make it a method of humanizing a rabbit antibody because Popkov *et al* teach the advantages of making humanized rabbit monoclonal antibodies as enunciated supra, but do not teach any method except making chimeric antibodies that contain complete rabbit variable regions that are more immunogenic than variable region humanized antibodies.

Claim 6 is included in this rejection because framework regions 1, 2 and 3 are discontiguous.

With regard to the inclusion of claim 3 in this rejection, although the art reference does not explicitly disclose identifying amino acid residues in a D-E loop region of the parent antibody and substituting only those amino acid residues that are not in the D-E loop, the D-E loop amino acid residues do not appear to be part of the framework amino acid residues, nor the CDR residues, and the art method teaches retention of the rabbit CDR residues while changing surface exposed framework residues. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 7 of copending Application No. 10/637,317 in view of US 20050048578 A1 and Morea *et al* (Methods 20: 267-279, 2000, IDS reference). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The claims of '317 do not teach substituting only those framework amino acid residues that are not proximal to a CDR, nor substituting only those amino acid residues that are not in the D-E loop, nor wherein the identifying step involves molecular modeling of the parent or non-human antibody, nor wherein the amino acid residues substituted are at least two discontiguous amino acid residues, nor wherein the rabbit antibody is from a rabbit homozygous for a VH allotype recited in instant claim12, nor wherein the binding affinity of the resurfaced antibody is that recited in instant claim 13.

US 20050048578 A1 discloses a method of making a humanized rabbit monoclonal antibody that is less immunogenic in a human, said method comprising resurfacing a rabbit monoclonal antibody (mAb), including a VH1-a3 allotype, by surface alignment comparison, *i.e.,* by comparing the amino acid sequences of the heavy and light chain variable regions with the most homologous human germline antibody genes, then predicting the surface residues in FR1, FR2 and FR3 of the most homologous human antibodies, identifying the rabbit framework residues at homologous positions, and substituting framework amino acid residues that are exposed in the rabbit mAb with the corresponding framework amino acid residues from the human antibody.
US 20050048578 A1 discloses that the framework regions have high homology to human sequences, and that the finding that rabbit antibody sequences can be readily aligned with human sequences shows that rabbit antibodies may be altered without substantially changing the conformation of rabbit antibody molecules, and thus retain the affinities of the modified rabbit antibodies. US 20050048578 A1 discloses changing Cys 80 in a parent mAb to the amino acid residue (Phe) found at position 80 of the human antibody. US 20050048578 A1 discloses making the humanized rabbit antibodies without substantially changing the conformation of the antibodies and further discloses use of the CAMEL modeling method to predict backbone conformations of all six CDRs and well as FR regions, and the interchain contact residues are expected to be non-surface exposed amino acid residues. US 20050048578 A1 discloses that it is preferable to produce an antibody that specifically binds to its corresponding antigen with a binding affinity of 10^{-8} M or more. US 20050048578 A1 exemplifies identifying amino acid residues of the framework region of the parent antibody that are not proximal to a CDR and substituting only those amino acid residues that are not proximal to said CDR, and teaches the importance of certain framework residues proximal to CDRs in maintaining the conformation of the CDRs and the affinity of the antibody, and identifying those residues located close to CDRs that may need to be preserved as rabbit residues in the humanized antibodies (especially [0059], [0016], [0148]-[0155], Figures 3 and 5, claim 3).

Morea *et al* teach resurfacing by comparing the sequences of the variable domains of a non-human antibody with human variable domains, and substituting the surface framework residues of the non-human antibody with the corresponding human residues. Morea *et al* teach maintaining antigen specificity and affinity of the non-human antibody that is resurfaced. Morea *et al* teach that key-site surface residues should not be changed, nor should antigen binding contact sites, nor should any residues be changed

that alter the structure of the antigen binding site. Morea *et al* teach that the advantage of resurfacing procedure over CDR grafting is that the design of the humanized antibody is much simpler and that, as only surface residues are mutated, the core of the non-human antibody variable domain is unchanged and consequently it is more likely that both the antigen binding loop conformations and their relative position in the resurfaced antibody are similar to those of the starting antibody. Morea *et al* teach molecular modeling of the variable domains, including the framework regions using as a template the domain of known structure with the highest sequence identity with the target domain (see entire article especially page 276 at column 2 starting at the first full paragraph and continuing through the first full paragraph on page 277, and page 272 at column 1 through page 274 at the first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of the claims of '317: to have substituted only those framework amino acid residues not proximal to a CDR as disclosed by US 20050048578 A1 and to have used molecular modeling as disclosed by US 20050048578 A1 and Morel *et al*, to have substituted at least two discontiguous amino acid residues as disclosed by US 20050048578 A1, to have made the humanized antibody with an affinity disclosed by US 20050048578 A1 that meets the limitation recited in instant claim 13, and to have used a rabbit antibody from a rabbit homozygous for the VH1-a1, 2 or 3 allotype disclosed by US 20050048578 A1 in order to compare a rabbit antibody with a light chain paired with a heavy chain of known allotypic specificity.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a humanized rabbit monoclonal antibody of high affinity and specificity as taught by the art references.

Claims 5 and 7 of '317 recite changing framework amino acid residues that include surface exposed amino acid residues.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-13 are directed to an invention not patentably distinct from claims 1-5 and 7 of commonly assigned 10/637,317 as enunciated supra.

16. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/637,317, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

17. Claim 6 is objected to because of the following informalities: Claim 6 contains a spelling error at line 2, *i.e.,* "discontiguous amino acid" should be "discontiguous amino acid**s**." Appropriate correction is required.

18. The reference crossed out in Applicant's Form 1449 filed 8/3/04 is a duplicate citation of a reference cited by Applicant in Applicant's Form 1449 filed 1/22/04.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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